REMARKS

Applicants respectfully request reconsideration upon continued examination of the present application on the merits based on the following reasons.

I. Status of the Claims

No claim amendments are made in this response. Claims 28-36, 39-40, 42-43, 51-60 and 64-72 are pending.

II. Rejection of Claims under 35 U.S.C. §103(a)

Claims 28-36, 39-40, 51-60 and 64-72 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge") in view of U.S. Patent No. 5,049,389 to Radhakrishnan ("Radhakrishnan"). Claims 42-43 remain rejected under 35 U.S.C. §103(a) for allegedly being obvious over Liversidge in view of Radhakrishnan and further in view of U.S. Patent No. 5,525,623 to Spear et al. ("Spear"). Applicants respectfully traverse each rejection. Spear is cited for the alleged teaching of a jet nebulizer or an ultrasonic nebulizer. Both rejections are addressed collectively for relying on the same primary and secondary references, Liversidge and Radhakrishnan.

A. The claimed species is non-obvious over the prior-art teaching of the genus.

Pursuant to MPEP 2144.08, a prior-art teaching of a genus does not necessarily render the claimed species obvious. "A determination of patentability under 35 U.S.C. 103 should be made upon the facts of the particular case in view of the totality of the circumstances . . . . The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)."

The Examiner is required to articulate many considerations, such as the size of the genus, the express teaching in the prior art, etc., to establish a *prima facie* case of obviousness. As submitted in the prior response, one skilled in the art would not have necessarily selected the claimed species, beclomethasone, as the active agent in view of the teachings of the cited art. *See* response filed on February 3, 2010, pages 8-9. In reply, the Examiner alleges that Applicants attacked the cited references individually. *See* final Office Action, the paragraph bridging pages 7-8 and page 8, first full paragraph. Applicants respectfully disagree.

Rather than individually attacking each cited reference, Applicants argue that neither cited reference provides any suggestion to one skilled in the art to combine the references. Applicants point out this deficiency in the rejection by providing a detailed analysis of each reference.

First, the primary reference, Liversidge, does not explicitly disclose beclomethasone or teach steroid as a preferred subgenus over other drug categories. Rather, Liversidge exemplified several drugs suitable for nanoparticulate active agent compositions. The relevant content of Liversidge is excerpted below:

> *Representative illustrative species of drug substances useful in the practice of this invention include:*
> *17-α-pregno-2,4-dien-20-yno-[2,3-d]-isoxazol-17-ol (Danazol);*
> *5α,17α-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17-ol (Steroid A);*
> *piposulfam;*
> *piposulfan;*
> *camptochecin;*
> *and ethyl-3,5-diacetoamido-2,4,6-triiodobenzoate*
>
> *In particularly preferred embodiments of the invention, the drug substance is a steroid such as danazol or Steroid A or an antiviral agent.*

Liversidge, column 4, lines 15-27. As such, a number of the drug species exemplified by Liversidge belong to categories other than steroids. The Examiner selected the exemplified

species, danazol and steroid A, and then generalized the teaching of the species to the subgenus of steroid, in an attempt to reach the species of the claimed invention. At a different level, Liversidge exemplified the drug categories of steroid and antiviral agent in parallel. The Examiner arbitrarily selected the subgenus steroid in the absence of any teaching or suggestion from the cited reference itself.

Second, in the absence of any reason from Liversidge to select steroid, the Examiner selected the secondary reference based on the teaching of Applicants' claimed invention. Because the claimed invention is directed to beclomethasone, Radhakrishnan is selected as the secondary reference to compensate for the deficiency of the primary reference. If Applicants had claimed a different steroid, a different secondary reference would have been selected. This rationale of combining the references is based on the improper hindsight and informed by Applicants' claimed invention because no teaching, suggestion or motivation to combine the references can be found in Radhakrishnan.

Radhakrishnan briefly discloses BECOTIDE®, which is an aqueous suspension of beclomethasone dipropionate administered by nebulization. As the Examiner expressly acknowledges, "BECOTIDE® is silent as to the particle size . . . of the suspended beclomethasone dipropionate particles" (final Office Action, page 6, first paragraph). Radhakrishnan also lacks any teaching or suggestion to further reduce the particle size of beclomethasone particles in BECOTIDE®. Rather, Radhakrishnan recommends solubilizing the steroids in a non-conventional liposome to obtain a modified release formulation. *See* column 8, lines 18-23, column 11, lines 43-45 and 64-68. In view of Radhakrishnan's disclosure, one skilled in the art would not have any reason to combine the teaching of Liversidge directed to particle size reduction.

Accordingly, Applicants did not attack the references individually other than pointing out that a reason to combine the references is not found in either reference.

In a related aspect, the Examiner asserts that Applicants attacked Radhakrishnan individually because Radhakrishnan is cited for its description of the commercially available BECOTIDE® rather than a teaching of the particle size of beclomethasone. This statement appears to be contrary to the Examiner's statements made in prior office actions. Specifically, in the non-final Office Action issued on November 12, 2009, the Examiner detailed the alleged teaching of Radhakrishnan as follows:

> *Radhakrishnan measured the liquid droplet particle size of aerosolized BECOTIDE® expressed as mass median aerodynamic particle size (MMAD) in units of microns (Figure 4). Radhakrishnan also demonstrates that particles with a size of less than 1.1 microns read the alveoli upon inhalation (Figure 3). According to Radhakrishnan's measurements, approximately 15% of the droplets have a particle size of about 400 nm or less and ~95% of the liquid droplets have a size of 10 microns or less (Figure 4 and col. 16, line 53 through col. 17, line 17).*

Non-final Office Action dated November 12, 2009, page 5, line 17, through page 6, line 2. In view of the Examiner's detailed analysis, Applicants responded that the particle size of Radhakrishnan reflects the droplet size of ***liposomes*** and therefore is not comparable with the particle size of beclomethasone ***solid particles*** of the claimed invention. In response, the Examiner commented that "Applicants' citation of Radhakrishnan's teachings of liposome formulations misconstrues the basis of the instant rejection and is off point." Final Office Action, page 11, lines 2-5.

Accordingly, Applicants respectfully request a clarification concerning the teaching of Radhakrishnan that is relied on for the rejection and how the teaching meets Applicants' claim elements.

The Examiner further asserts that Applicants' "cherry-picked" the decision in *Takeda v. Alphapharm* because *Takeda*'s facts are not analogous to the facts of the rejection of the claimed invention. Applicants agree with the Examiner that one of the cited references of *Takeda* teaches

away from selecting compound b in Takeda. However, Applicants note that the district court "first concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that the prior art taught away from its use" (*Takeda Chemical Industries v. Alphapharm Pty.*, 492 F.3d 1350, 1354 (Fed. Cir. 2007)). The district court's conclusion was affirmed by the reviewing court. Therefore, the court of *Takeda* relied upon two factors to hold that the invention was nonobvious over the cited art: (1) lack of a motivation in the prior art and (2) a teaching away in the prior art. The first factor is analogous to the prior art cited against the claimed invention.

B. The rejection relies on an improper "obvious-to-try" rationale.

At best the Examiner has established an "obvious-to-try" rationale, which must be supported by a reasonable expectation of success.

The subgenus of steroid encompass hundreds of compounds. A search of "steroid" in the McSH database of National Center for Biotechnology Information (NCBI) returned 112 entries. In the absence of any teaching or suggestion from the prior art that a stable nanoparticulate beclomethasone composition can be made, one skilled in the art would have to try each and every steroid in an attempt to obtain a stable nanoparticulate steroid composition.

A suggestion to try each species of the subgenus is explicitly rejected as a proper application of "obvious-to-try" rationale in the recent Federal Circuit ruling, excerpted below:

> *To differentiate between proper and improper applications of "obvious to try," this court outlined two classes of situations where* ***"obvious to try" is erroneously equated with obviousness under §103****. In the first class of cases, what would have been "obvious to try" would have been to vary all parameters or* ***try each of numerous possible choices*** *until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.*

In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988); (emphasis added). *Kubin* further analogizes this rejection rationale with "throw[ing] metaphorical darts at a board filled with combinatorial prior art possibilities" with the aid of hindsight, and therefore, is improper. *Id.*

In the prior response, Applicants further quoted Liversidge to support the conclusion that a reasonable expectation of success is lacking. *See* page 9. In reply, the Examiner contends that Applicants' argument "is unpersuasive, because it is not based on any objective evidence, but rather on Applicants' unsupported assertions." Final Office Action, the paragraph bridging pages 9 and 10. Contrary to the Examiner's contention, Applicants did not make a mere statement to rebut the rejection. Rather, Applicants quoted Liversidge, which is a reference cited by the Examiner, to substantiate the argument.

The Examiner further asserts that "absolute expectation of success is not . . . required" since "Liversidge sets forth a simple screening method to ascertain whether a particular drug/surface stabilizer combination would yield a stable composition." Final Office Action, page 10, lines 2-7. Applicants respectfully disagree.

Liversidge's simple screening method is for selecting an optimal surface stabilizer for a ***given*** active agent. The first step of the screening method is to disperse coarse particles of "a ***selected*** drug substance of interest" (column 7, lines 27-28). In the absence of any knowledge that a stable nanoparticulate composition for a particular active agent, such as beclomethasone, could be obtained, the screening method for a optimal surface stabilizer cannot be applied.

C. The claimed invention is nonobvious in view of the unexpected results.

(i) The claimed invention achieved unexpected results in comparison to BECOTIDE® as described by Radharkrishnan.

The Examiner cites Radharkrishnan for the alleged teaching of an aerosol beclomethasone composition. In fact, Radharkrishnan teaches away from developing aerosols of

solid particles for delivery to the lung, as prescribed by claim 28. For instance, column 4 lines 55-60 state that "Because of their poor solubility in aqueous systems, formulating a steroid in an aqueous solvent requires adding solubilizing agents such as ionic surfactants, cholates....or other solubilizers or using micronized suspension (sic) of crystalline drug." Radhakrishnan recommends against these alternatively delivery approaches because the additives, "particularly when used for inhalation, have undesirable effects." Column 4, lines 60-65. Later in column 5, lines 42-51, Radhakrishnan describes BECOTIDE® as "a suspension of beclomethasone dipropionate in an aqueous medium....(that) has only 50 μg/mL of the active ingredient and has very poor, if any, alveolar deposition." Radhakrishnan goes on to suggest that 50 μg/mL is the maximum formulable BDP in an aqueous medium, and as such does not provide a sufficient therapeutic amount of steroid to treat sarcoidosis or IPF. Column 5, lines 48-51. The teaching of Radhakrishnan taken as a whole suggests that nebulization of aqueous suspensions of crystalline drug is likely to be inefficient and ineffective for delivering drug to the lung. As recited by claim 39, the amount of the therapeutic agent is from 0.1% to 60%. Example 1 further illustrates a nanoparticulate beclomethasone composition comprising 0.2% of beclomethasone, which is equivalent to 2000 μg/mL of beclomethasone, substantially higher than the "maximum formulable BDP" of 50 μg/mL disclosed by Radharkrishnan. Therefore, one skilled in the art would not have expected to develop a concentrated suspension of BDP for nebulization based on the prior-art teachings.

Moreover, in Table XI (column 32, lines 51-69) Radharkrishnan reports the results of a cascade impactor study of BECOTIDE®. The amount of drug reaching the impactor (stage 0 through the filter) is 8.1 μg out of a total of 194.4 μg. Thus, the fraction of BDP reaching the impactor was about 4.2%. In comparison, the amounts of nanoparticulate BDP reaching the impactor in the claimed invention ranged from 17 to 35% (a 4- to 8-fold improvement over BECOTIDE®). *See* the accompanying declaration, Table 2. Based on the results obtained by Radharkrishnan, one skilled in the art would not have been able to develop an aerosol of crystalline BDP because of the poor delivery efficiency observed in that study.

Consequently, Radhakrishnan proposes to solve the problems associated with inefficient nebulization of aqueous crystalline suspensions of steroids by dissolving the drugs and incorporating them into liposomes. Taken in its entirety, Radhakrishnan suggests to one skilled in the art that nebulization of crystalline suspensions is not technically feasible, and therefore a different solution had to be found. Accordingly, the claimed invention is non-obvious over the combination of the cited art.

(ii) The claimed invention achieved unexpected results in comparison to a microparticulate beclomethasone formulation.

As evidenced by the declaration submitted herewith, the claimed invention directed to a nanoparticulate beclomethasone composition achieved unexpected results in comparison to delivery of a microparticulate beclomethasone composition. In particular, an aerosol formulation of a nanoparticulate beclomethasone composition was compared to an aerosol of a micronized beclomethasone composition. The comparison determined how much drug each formulation successfully delivered to a target (e.g., a patient) when the compositions were administered via an aerosol nebulizer.

An aerosol nebulizer is a standard medical device used to delivery drugs to the respiratory tract. However, one problem encountered with prior art formulations is that a significant amount of active agent remains in the nebulizer rather than being delivered to the subject when the aerosol is pumped or activated. Surprisingly, Applicants' claimed composition addresses this problem present in the prior art. Specifically, the results of the comparison study described in the declaration show that a higher percentage of the micronized beclomethasone remained in the aerosol nebulizer as compared to the nanoparticulate beclomethasone compositions.

Three nanoparticulate beclomethasone formulations were tested: Formulations II, III, and IV (the microparticulate beclomethasone formulation is designated Formulation I). Table 2 of the declaration, which shows the nebulization output for each formulation, is reproduced below. The nanoparticulate beclomethasone formulations showed *an increase* in the amount of drug

delivered to the impactor (which correlates with the amount of drug delivered to a patient), as compared to the microparticulate formulation, of **up to 337%** (125% for Nano II, 112.5% for Nano III, and 337.5% for Nano IV). Moreover, the nanoparticulate beclomethasone formulations showed ***a decrease*** in the amount of drug remaining in the nebulizer, as compared to the microparticulate formulation, of **up to 67%** (13.5% for Nano II, 30% for Nano III, and 67% for Nano IV).

Table 2

Formulation	BDP Fraction Remaining	BDP Fraction on Impactor
Micro I	~89%	~8%
Nano II	~77%	~18%
Nano III	~62%	~17%
Nano IV	~29%	~35%

The results of the comparison study are significant as drug remaining in a delivery device, such as an aerosol nebulizer, does not reach a patient and therefore provides no therapeutic results. Moreover, a composition in which only a portion of drug is actually delivered to a patent is undesirable as a patient can receive inconsistent dosages of drug.

Accordingly, the rejection under 35 U.S.C. §103(a) should be withdrawn in view of the unexpected results.

III. Provisional Double Patenting Rejection

Claims 28-33, 39-40, 51-60, 66, 69 and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-7, 9-11 and 13-14 of copending Application No. 10/035,324 in view of Liversidge and Radhakrishnan. Claims 28-33, 53-60, 66, 69 and 72 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 60-61, 64-65, 69-70 and 72-76 of copending Application No. 10/768,194 in view of Liversidge and Radhakrishnan. Claims 28-36 and 51-60 remain provisionally rejected

on the ground of nonstatutory obviousness-type double patenting over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge and Radhakrishnan. As the rejections are provisional at this stage, Applicants choose to defer any action until the Examiner indicates that the claims at issue are otherwise allowable.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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